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In This Issue

Pegfilgrastim (Neulasta™): A Brief Review

By David R. Kohler, Pharm.D.

Pegfilgrastim is a covalent conjugate of recombinant methionyl human filgrastim and monomethoxypolyethylene glycol (PEG). Filgrastim is a water-soluble 175-amino acid protein with a molecular weight of approximately 19 kiloDaltons that is obtained from the bacterial fermentation of a strain of *Escherichia coli* transformed with a genetically engineered plasmid containing the human filgrastim gene. To produce pegfilgrastim, a 20-kD monomethoxypolyethylene glycol molecule is covalently bound to the N-terminal methionyl residue of filgrastim.

Description

Neulasta™ (NDC 55513-190-01) is supplied as a preservative-free solution containing 6 mg pegfilgrastim/0.6 mL in a single-use syringe with a 27-gauge, ½-inch needle and an UltraSafe® Needle Guard. Each syringe contains 6 mg pegfilgrastim (based on protein weight), in a sterile, clear, colorless, preservative-free solution (pH = 4.0) containing acetate (0.35 mg), sorbitol (30 mg), polysorbate 20 (0.02 mg), and sodium (0.02 mg) in water for injection, USP.

Neulasta™ should be stored under refrigeration at 2°–8°C (36°–46°F); syringes should be kept in their carton to protect from light until time of use. Avoid shaking the syringes. Before injection, Neulasta™ may be allowed to reach room temperature for a maximum of 48 hours, but should be protected from light. Neulasta™ left at room temperature for more than 48 hours should be discarded. Freezing should be avoided; however, if accidentally frozen, Neulasta™ should be allowed to thaw in the refrigerator before administration. If frozen a second time, Neulasta™ should be discarded.[1]

FDA-approved Indications

Pegfilgrastim (Neulasta™) has a single FDA-approved indication that it shares with filgrastim, ". . . to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive antineoplastic drugs associated with a clinically significant incidence of febrile neutropenia."[1]

Pharmacology

Both filgrastim and pegfilgrastim are colony stimulating factors that bind to hematopoietic cell surface receptors, thereby stimulating proliferation, differentiation, commitment, and end cell functional activation. Studies on cellular proliferation, receptor binding, and neutrophil function demonstrate that filgrastim and pegfilgrastim have the same mechanism of action.[1] Data from normal volunteers indicate that mobilization of CD34+ cells and progenitors may occur in a more timely manner and to around the same absolute numbers as with repeated daily injections of unmodified filgrastim.[2] Pegfilgrastim serum concentrations were sustained until neutrophil nadirs occurred, and then declined rapidly as neutrophils started to recover, consistent with a self-regulating neutrophil-mediated clearance mechanism. The safety profiles of pegfilgrastim and filgrastim were similar.

Pharmacokinetics

Pegfilgrastim (Neulasta™) pharmacokinetics were non-linear in 379 patients with cancer, in whom clearance varied inversely with dose. The apparent clearance of pegfilgrastim is dose dependent (26.4–40.9 mL/h per kg after a 30-µg/kg dose, 23.8 mL/h per kg following 60 µg/kg, 6.7–7.92 mL/h per kg following 100 µg/kg, and 2.19–5.06 mL/h per kg following 300 µg/kg). Pegfilgrastim serum concentrations were sustained until the neutrophil nadir occurred then declined rapidly as neutrophil count recovered.[3]

Neutrophil receptor binding mediates pegfilgrastim clearance from serum and is directly related to the number of neutrophils; i.e., pegfilgrastim concentration declines rapidly at the onset of neutrophil recovery that follows myelosuppressive chemotherapy.[4] Body weight also affects systemic exposure and clearance in direct proportion to pegfilgrastim dose.[5] The half-life of Neulasta™ ranged from 15–80 hours after subcutaneous (SC) injection. Pegfilgrastim has reduced renal clearance and prolonged persistence *in vivo* as compared to filgrastim.[1]

No gender-related differences have been observed in Neulasta™ pharmacokinetics and no differences were observed in the pharmacokinetics of elderly patients (≥65 years of age) compared to younger patients (<65 years of age). Pegfilgrastim's pharmacokinetic profile has not yet been adequately evaluated in pediatric populations or in patients with hepatic or renal insufficiency.

Selected Clinical Studies

A randomized, double-blind study was designed to compare the safety and efficacy of filgrastim 5 µg/kg body weight administered once daily and pegfilgrastim 100 µg/kg once, every 21-day chemotherapy cycle in 152 women with advanced (stages II–IV) breast cancer who were treated with doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2. The study's primary endpoint was the duration of severe neutropenia during the first of four cycles. Secondary endpoints included the duration of severe neutropenia during three cycles, the absolute neutrophil count (ANC) profile, time to absolute neutrophil count recovery, and safety. Severe neutropenia occurred for 0–2 days during the first treatment cycle in 37%, 67%, and 89% of patients who received pegfilgrastim 30, 60, and 100 µg/kg, respectively, compared to 88% of patients who received filgrastim. Severe neutropenia occurred for three to five days during cycle one in 63%, 34%, and 11% of patients who received pegfilgrastim 30, 60, and 100 µg/kg, respectively, compared to 12% of patients who received filgrastim. Safety was similar with both drugs.[3]

The safety and efficacy of filgrastim and pegfilgrastim were compared in a randomized, double-blind study in 310 patients with advanced (stages II–IV) breast cancer who received doxorubicin 60 mg/m^2 and docetaxel 75 mg/m^2 every 21 days for four cycles. Patients were randomly assigned to receive either daily filgrastim 5 µg/kg body weight or pegfilgrastim 100 µg/kg once, plus a daily placebo injection starting 24 hours after chemotherapy administration. Placebo and filgrastim injections were given daily until patients' ANC was >10 x 10^9/L, or a total of 14 days. The mean number of filgrastim injections was 11/cycle. The study's primary endpoint was the duration of severe neutropenia (<0.5 x 10^9/L) during the first of four cycles. The incidence of severe neutropenia during the first cycle was 79% in the filgrastim group and 77% in the pegfilgrastim group. The average duration of severe neutropenia was similar in both groups (1.76 days with filgrastim and 1.73 days with pegfilgrastim. The mean durations of severe neutropenia during the second through fourth cycles were 0.7, 0.6, and 0.9 days for pegfilgrastim and 1.1, 1.2, and 1.3 days for filgrastim, respectively. The incidence of febrile neutropenia (fever ≥38.2°C + ANC <0.5 x 10^9/L) was 12% with filgrastim and 7% with pegfilgrastim during the first cycle, and 18% and 9% for filgrastim- and pegfilgrastim-treated patients during the entire study. The time to ANC recovery (2 x 10^9/L) was 9.3 days for pegfilgrastim-treated patients and 9.7 days for filgrastim-treated patients.[4]

Thirteen patients with non-small-cell lung cancer were randomly assigned to receive daily filgrastim 5 µg/kg or a single injection of pegfilgrastim 30, 100, or 300 µg/kg two weeks before chemotherapy and again 24 hours after carboplatin and paclitaxel. Peak pegfilgrastim serum concentrations and the duration of increased serum concentrations were dependent on the administered dose. Pegfilgrastim concentrations remained increased longer in patients with chemotherapy-induced neutropenia. In patients who received pegfilgrastim two weeks before chemotherapy, median ANC and the duration of increased ANC increased in a dose-dependent fashion. After chemotherapy, median ANC nadirs were similar in the cohorts that received filgrastim and pegfilgrastim 30 µg/kg. Pegfilgrastim 100 µg/kg and 300 µg/kg increased ANC and mobilized CD34+ cells comparably or greater than the effects achieved with daily filgrastim.[6]

Pegfilgrastim was evaluated in an open-label study in 30 newly-diagnosed patients with non-Hodgkin's lymphoma who received CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone). Patients received a single dose of pegfilgrastim 6 mg subcutaneously 24 hours after cytotoxic chemotherapy. Participating patients had a mean weight of 81.2 ±20.6 kg. Grade 4 neutropenia occurred in 43% of patients (12 of 28), with a mean duration of one day. The median time to ANC recovery was 10 days. Febrile neutropenia occurred in 11% of patients who completed the study. A statistically significant effect of body weight on the duration of neutropenia was not observed; however, the duration of grade 4 neutropenia was 0.9 days for patients who weighed > 78 kg and 1.1 days for patients weighed < 78 kg.[7]

Adverse Effects

FDA approval was based on safety data from 465 subjects with lymphoma and solid tumors (breast, lung, and thoracic tumors) enrolled in six randomized clinical studies. Subjects received Neulasta™ after nonmyeloablative cytotoxic chemotherapy. Most adverse experiences were attributed by the investigators to the underlying malignancy or cytotoxic chemotherapy and occurred at similar rates in subjects who received Neulasta™ (n = 465) or daily filgrastim injections (n = 331). Adverse experiences occurred at rates between 72% and 15% and included: nausea, fatigue, alopecia, diarrhea, vomiting, constipation, fever, anorexia, skeletal pain, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, dizziness, granulocytopenia, stomatitis, mucositis, and febrile neutropenia.[1]

The most common adverse event attributed to Neulasta™ in clinical trials was medullary bone pain, generally of mild-to-moderate severity. Bone pain was reported in 25% of subjects, which is comparable to the incidence in filgrastim-treated patients.[4] Approximately 12% of all subjects used non-opioid analgesics and less than 6% required opioid analgesics in association with bone pain. Product labeling indicates that no patients withdrew from a study due to bone pain.[1] The Pegfilgrastim Study Group retrospectively compared the differences in bone pain symptoms and characteristics between patients who received daily filgrastim injections and those who received a single dose of pegfilgrastim.[8] Among patients who reported bone pain, there was a trend toward earlier onset with pegfilgrastim; however, symptoms were not associated with either increased pain severity or duration. The investigators also noted that the overall incidence of bone pain did not differ among patients who received a fixed 6-mg pegfilgrastim dose or pegfilgrastim 100 µg/kg of body weight for three weight strata (<60 kg, 60–100 kg, or >100 kg). They found that the incidence, severity, duration, and time to bone pain onset were similar for filgrastim and pegfilgrastim, whether pegfilgrastim dose was calculated by weight or given at a fixed dose.[8]

Hematologic Effects

In clinical studies, leukocytosis (WBC counts >100 x 10^9/L) was observed in <1% of 465 subjects with non-myeloid malignancies who received Neulasta™. Leukocytosis was not associated with any adverse events.[1]

Rare, and in some cases, fatal splenic rupture has been reported following filgrastim administration for peripheral blood progenitor cell (PBPC) mobilization in patients with cancer and in healthy PBPC donors. Neulasta™ should not be used for PBPC mobilization. Patients who receive pegfilgrastim who report left abdominal or shoulder tip pain should be evaluated for splenic enlargement and rupture.

Severe sickle cell crises have been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle/ß+ thalassemia) who received filgrastim for PBPC mobilization or following chemotherapy. Pegfilgrastim should be used cautiously in patients with sickle cell disease. Patients with sickle cell disease who received pegfilgrastim should be kept well hydrated and monitored for the occurrence of sickle cell crises. In the event of severe sickle cell crisis, supportive care should be administered and interventions to ameliorate the underlying event should be considered, such as therapeutic erythrocyte exchange transfusion.

Pulmonary Effects

Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis who received filgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving pegfilgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS.[1]

Metabolic Effects

Reversible, increased LDH, alkaline phosphatase, and uric acid were observed in clinical trials, none of which required intervention.[6] The incidence of these changes for Neulasta™ relative to filgrastim, were: LDH (19% vs. 29%), alkaline phosphatase (9% vs. 16%), and uric acid (8% vs. 9%). One-percent of reported cases were classified as severe for both treatment groups.[1]

Immunogenicity

Pegfilgrastim is potentially immunogenic; however, the incidence of antibody development in patients who received Neulasta™ has not been adequately determined. Although available data suggest that a small proportion of patients develop binding antibodies to filgrastim or pegfilgrastim, the nature and specificity of the antibodies has not been adequately studied. No neutralizing antibodies were detected by a cell-based bioassay in 46 patients who apparently developed binding antibodies. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay, and the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. At present, comparison of the incidence of antibodies to Neulasta™ with the incidence of antibodies to other products may be misleading.[1]

Allergic-type reactions have been reported with filgrastim, including anaphylaxis, skin rash, and urticaria, during initial or subsequent exposure. In some cases, symptoms recurred with rechallenge, which suggests a causal relationship.[1]

Cytopenias resulting from an antibody response to exogenous growth factors have been reported rarely in patients treated with other recombinant growth factors. Although there is a theoretical possibility that an antibody

directed against pegfilgrastim may cross-react with endogenous granulocyte-colony stimulating factor (G-CSF), resulting in immune-mediated neutropenia, the phenomenon not been observed in clinical studies.[1]

Potential Effect on Malignant Cells

Pegfilgrastim is a growth factor that stimulates primarily neutrophils and neutrophil precursors; however, the G-CSF receptor has been found on tumor cell lines, including some myeloid, T-lymphoid, lung, head and neck, and bladder tumor cell lines. The possibility that pegfilgrastim may stimulate growth for some tumor types cannot be excluded. Neulasta™ use has not been studied in myeloid malignancies and myelodysplasia.[1]

Drug Interactions

Drug interaction studies between pegfilgrastim and other drugs have not been performed. Drugs such as lithium may potentiate the release of neutrophils. The manufacturer recommends frequent monitoring of neutrophil counts for patients who receive lithium and pegfilgrastim concurrently.[1]

Precautions and Contraindications:

Neulasta™ is contraindicated in patients with known hypersensitivity to *E. coli*-derived proteins, pegfilgrastim, filgrastim, or any other component of the product.

Use in Infants and Adolescent Patients

The 6-mg fixed dose formulation has not been adequately studied and should not be used in infants, children, and adolescents weighing <45 kg.[1]

Use in Elderly Patients

No overall differences in safety or effectiveness were observed between elderly patients (aged >65 y) and younger patients; however, due to the small number of elderly subjects, small but clinically relevant differences cannot be excluded.[1]

Dosage and Administration

Pegfilgrastim (Neulasta™) is indicated for administration only by subcutaneous injection.[1]

Neulasta™ 6 mg subcutaneously is given once per chemotherapy cycle. Neulasta™ should not be administered within 14 days before cytotoxic chemotherapy or <24 hours after chemotherapy.[1]

Neulasta™ has not been studied in patients receiving chemotherapy associated with delayed myelosuppression (e.g., nitrosoureas, mitomycin) or in patients receiving radiation therapy. Neulasta™ administered concomitantly with fluorouracil or other antimetabolites has not been evaluated in patients. Pegfilgrastim administered at 0, 1, and 3 days before fluorouracil resulted in increased mortality in mice; administration of pegfilgrastim 24 hours after fluorouracil did not adversely affect survival.[1]

Product packaging for Neulasta™ includes an UltraSafe® Needle Guard, a safety device designed to prevent accidental needle sticks after pegfilgrastim administration. The UltraSafe® Needle Guard, is activated by placing both hands behind the needle, grasping the guard with one hand, and sliding the guard forward until the needle is completely covered and the guard clicks into place. If an audible click is not heard, the needle guard may not be completely activated. The manufacturer recommends discarding used syringes by activating the needle guard and placing the syringe into an approved puncture-proof container.[1]

Maximum Dose

The maximum amount of Neulasta™ that can be safely administered in single or multiple doses has not been determined. Single doses of 300 µg/kg have been administered subcutaneously to eight normal volunteers and three patients with non-small cell lung cancer without serious adverse effects. These subjects experienced a mean maximum ANC of 55×10^9 cells/L, with a corresponding mean maximum WBC of 67×10^9 cells/L. The absolute maximum ANC observed was 96×10^9 cells/L with a corresponding absolute maximum WBC = 120×10^9/L. The duration of leukocytosis ranged from 6–13 days. Leukapheresis should be considered to manage hyperleukocytosis in symptomatic individuals.[1]

Cost

A single subcutaneous injection of pegfilgrastim 6 mg stimulates granulopoiesis for a period of between one to two weeks.

Cost comparison between pegfilgrastim 6 mg/0.6 mL x1 dose and filgrastim (5 µg/kg per day x10 days:

PEGFILGRASTIM (single, fixed dose) $1,711.88

FILGRASTIM (5 µg/kg per day for 11 days) Cost Table

Patient's Body Weight	Number and Size of Vials Needed/Dose	DAILY Cost to Pharmacy	Cost to Pharmacy for 11 doses
≤ 66kg	1 x 300 µg	$104.705	$1,151.76
66.1–105.6 kg	1 x 480 µg	$165.308	$1,818.39
105.7–132 kg	2 x 300 µg	$209.41	$2,303.51
133–172 kg	1 x 300 µg + 1 x 480 µg	$270.013	$2,970.14

Patient Counseling

Drug Name

PEGFILGRASTIM (peg-fill-GRASS'-tim) INJECTION or NEULASTA™

- Used to prevent infections caused by cancer chemotherapy.

When You Should Not Use This Medicine

- You should not use this medicine if you have had an allergic reaction to pegfilgrastim, or to similar medicines such as filgrastim (Neupogen®).
- You should not use this medicine if it has been less than 24 hours since you last received chemotherapy, or if your next chemotherapy treatment is fewer than 14 days away.

How to Use and Store this Medicine

- This medicine is given as a shot under your skin, usually as one injection during each of your chemotherapy treatment cycles.
- Usually a nurse or other trained health professional will give you this medicine, but a home health care-giver may also give it.
- Your physicians, nurses, or other health care providers will show you the body areas where this shot can be given.
- You should use a different body area each time you give yourself a shot and keep track of where you give each shot to make sure you inject the medicine at different sites.
- Throw away used needles and syringes in a hard, closed container that the needles cannot poke through.
- If you store this medicine at home, keep it in the refrigerator. Do not freeze or shake the medicine.
- Leave the medicine in its carton until you are ready to use it.
- You may leave the medicine at room temperature for up to 48 hours before giving the shot, but keep the medicine away from heat or direct light.

If You Miss a Dose

- If you miss a dose or forget to use your medicine, call your doctor for instructions.

Warnings

- This medicine may make you dizzy or drowsy. Avoid driving, using machines, or doing anything else that could be hazardous if you are not alert.
- Your doctor will need to check your progress at regular visits while you are using this medicine.

Side Effects

Call your doctor right away if you have any of these side effects:

- Allergic reaction: Itching or hives, swelling in face or hands, swelling or tingling in the mouth or throat, tightness in chest, trouble breathing;
- Lightheadedness or fainting;
- Slow or shallow breathing, or a sudden sharp pain in your left upper stomach or shoulder area.

If you have problems with these less serious side effects, talk with your doctor:

- Swelling in your hands, ankles, or feet;
- Unusual bleeding, bruising;
- Muscle, joint, or bone pain;
- Swelling, bruising, pain, or a hard lump where the shot is given.

If You Have Other Side Effects That You Think are Caused by this Medicine, Tell Your Doctor.

Black-Box Warnings

None for this drug product.

Conclusion

Pegfilgrastim offers advantages over filgrastim with respect to patient compliance. It simplifies hematopoietic growth factor support for patients by replacing a need for repeated daily injections for variable periods with a single fixed dose. In addition, pegfilgrastim simplifies hematopoietic growth factor support for health care providers by eliminating [1] a need to train ambulatory outpatients or their personnel caregivers in subcutaneous injection techniques, [2] repeated visits to receive injections for patients who cannot self administer an injectable drug, and [3] repeated daily injections for institutionalized patients.

Acquisition costs are comparable to a 10–12-day course of daily filgrastim injections using weight-based dosing (5 µg/kg per day) for the majority of adult patients who require prophylaxis against chemotherapy-associated neutropenia; i.e., with body weight between 66 kg and 105 kg. Pegfilgrastim may be expected to reduce total costs relative to filgrastim for its approved indication.

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Selected FDA Safety Alerts

Abbokinase (urokinase)

Audience: Cardiologists, Intensivists, and other healthcare professionals

FDA and Abbott announced the reintroduction of Abbokinase (urokinase) for use in the lysis of massive pulmonary emboli and pulmonary emboli accompanied by unstable hemodynamics. The WARNINGS section of the labeling has been strengthened to include post-marketing reports of anaphylaxis, other infusion reactions, and class information regarding the potential for cholesterol embolization. The ADVERSE REACTIONS section of the product labeling reflects the analysis of post-marketing safety data.

Accutane (isotretinoin)

Audience: Dermatologists and other healthcare professionals

FDA and Roche revised the **WARNINGS:** Psychiatric Disorders, Boxed **CONTRAINDICATIONS AND WARNINGS, DOSAGE AND ADMINISTRATION,** and **PRECAUTIONS:** Drug Interactions sections of the prescribing information. Changes in pediatric labeling were made to the **CLINICAL PHARMACOLOGY:** *Special Patient Populations: Pediatric Patients,* **WARNINGS:** *Skeletal: Bone Mineral Density,* and **PRECAUTIONS:** *Pediatric Use* sections.

Aggressive and/or violent behaviors have been added to the list of events that Accutane may cause, based on post-marketing safety reports. No mechanism of action has been established for these events. A new table has been added to clarify those circumstances where pregnancy tests and Accutane Qualification Stickers are applicable. Information specific to pediatric patients has been added based on the results of recent studies conducted in this patient population. A statement has been added regarding the long-term use of Accutane advising that Accutane be given at the recommended doses for no longer than the recommended duration. Prescribers were advised to exercise caution when systemic corticosteroids or phenytoin are used with Accutane.

Alpha Interferons

Intron A (Interferon alfa 2b, recombinant)
Rebetron Combination Therapy (Rebetrol (Ribavirin, USP) Capsules and Intron A)
Roferon-A (Interferon alfa-2a, recombinant)

Audience: Oncologists and other Healthcare professionals

Healthcare professionals are advised of important safety information for all alpha interferons. A BOXED WARNING has been added regarding the occurrence of neuropsychiatric, autoimmune, ischemic, and infectious disorders in patients taking alpha interferons; additional safety information and direction for patient monitoring is also provided in the WARNINGS section of the prescribing information.

Bextra (valdecoxib)

Audience: Rheumatologists and other healthcare professionals

FDA and Pharmacia/Pfizer strengthened the **CONTRAINDICATIONS, WARNINGS, and ADVERSE REACTIONS** sections of the prescribing information. In postmarketing experience, rare reports of hypersensitivity reactions (i.e, anaphylatic reactions and angioedema) and skin reactions, including cases of Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, and erythema multiforme, have been received. These cases, some of which were serious/life threatening, have occured in patients with and without a history of allergic type reations to sulfonamides.

Cafergot (ergotamine tartrate and caffeine)

Audience: Neurologists and other healthcare professionals

FDA and Novartis strengthened the labeling, including a new **BOXED WARNING** and updates to the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and CLINICAL PHARMACOLOGY** sections of the prescribing information.

Serious and/or life-threatening peripheral ischemia has been associated with the coadministration of Cafergot with potent CYP 3A4 inhibitors including protease inhibitors and macrolide antibiotics. Because CYP 3A4 inhibition elevates the serum levels of Cafergot, the

risk for vasospasm leading to cerebral ischemia and/or ischemia of the extremities is increased. Because of the increased risk of serious vasospastic adverse events, concomitant use of these medications is contraindicated.

Camptosar (irinotecan hydrochloride)

Audience: Oncologists and others caring for patients with metastatic colorectal cancer

The prescribing information in the BOXED WARNING, WARNINGS, and PRECAUTIONS sections were revised to identify patients at higher risk of severe toxicity, to clarify dose modification guidelines, and to augment information about management of treatment-related toxicities, including severe and occasionally life-threatening diarrhea.

Clozaril (clozapine)

Audience: Psychiatrists, Pharmacists

FDA and Novartis have strengthened the BOXED WARNING and WARNINGS sections of the prescribing information (PI) for Clozaril (clozapine) as follows: (1) The previously existing BOXED WARNING has been relocated to the beginning of the PI and revised to advise health care providers of the association of myocarditis with clozapine therapy; (2) A subsection has been added to the WARNINGS section entitled "Myocarditis" to provide data and clozapine treatment guidelines related to this issue.

Depakote / Depakene / Depacon (divalproex sodium / valproic acid / valproate sodium)

Audience: Neuropsychiatric healthcare professionals

FDA and Abbott strengthened the CONTRAINDICATIONS, WARNINGS and PRECAUTIONS sections of the label for Depakote Tablets, Depakote ER Tablets, Depakote Sprinkle Capsules, Depakene Capsules and Syrup and Depacon for Injection. Healthcare professionals were informed that hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with urea cycle disorders [UCD], a group of uncommon genetic abnormalities. Patient criteria to consider in evaluation for UCD prior to initiation of valproate therapy are offered.

Lariam (mefloquine hydrochloride)

Audience: Infectious disease and other healthcare professionals

FDA and Roche strengthened the CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the label. Healthcare professionals were notified that Lariam is contraindicated for prophylaxis in patients with active depression, a recent history of depression, generalized anxiety disorder, psychosis, schizophrenia or other major psychiatric disorders, or with a history of convulsions. During prophylactic use, if psychiatric symptoms such as acute anxiety, depression, restlessness or confusion occur, these may be considered prodromal to a more serious event. In these cases, the drug must be discontinued and an alternative medication should be substituted.

Lovenox (enoxaparin sodium)

Audience: Healthcare Professionals

FDA and Aventis strengthened the WARNINGS and PRECAUTIONS sections of the Lovenox prescribing information to inform healthcare professionals that the use of Lovenox Injection is not recommended for thromboprophylaxis in patients with prosthetic heart valves. New postmarketing safety information concerning congenital anomalies and non-teratogenic effects on pregnant women and fetuses are described.

Nolvadex [tamoxifen citrate]

Audience: Oncologists and other healthcare professionals caring for women with breast cancer

FDA and AstraZeneca added a boxed warning and strengthened the WARNINGS section of the label to inform healthcare professionals about new risk information of particular relevance to women with ductal carcinoma in situ [DCIS] and women at high risk for developing breast cancer and are receiving or considering Nolvadex therapy to reduce their risk of developing invasive breast cancer.

Serious, life-threatening or fatal events associated with Nolvadex in the risk reduction setting [women at high risk for cancer and women with DCIS] include endometrial cancer, uterine sarcoma, stroke, and pulmonary embolism. Healthcare providers should discuss the potential benefits versus the potential risks of these serious events with women considering Nolvadex to reduce their risk of developing breast cancer.

PVC Devices Containing the Plasticizer DEHP

Audience: Hospital Risk Managers and other healthcare professionals

FDA's Center for Devices and Radiological Health posted a safety assessment of Di(2-ethylhexyl) phthalate (DEHP) released from polyvinyl chloride (PVC) medical devices. Healthcare professionals were advised of steps that can be taken to reduce the risk of exposure in certain populations.

Rapamune (sirolimus)

Audience: Transplantation Surgeons and other healthcare professionals

FDA notified healthcare professionals of a "Dear Health Care Provider" letter issued April 24, 2002 by Wyeth, sent to members of the American Society of Transplantation and The American Society of Transplant Surgeons. The letter informs clinicians of the risk of hepatic artery thrombosis, graft loss, and death associated with the use of Rapamune (sirolimus) in de novo liver transplantation.

Seroquel (quetiapine fumarate)

Audience: Neuropsychiatric healthcare professionals and Pharmacists

AstraZeneca received reports of medication errors involving confusion between its atypical antipsychotic Seroquel (quetiapine fumarate), indicated for the treatment of schizophrenia, and Serzone (nefazodone hydrochloride), a product of Bristol-Myers Squibb, indicated for the treatment of depression. In addition to the similarity in names between Seroquel and Serzone, the overlapping strengths (100 mg and 200 mg), the dosage forms (tablets), the dosing interval (BID), and the fact that these two products were stocked close together in pharmacies were also critical in causing these errors.

Serzone (nefazodone HCL)

Audience: Psychiatrists, Pharmacists

FDA and BMS added a Black Box Warning and strengthened the WARNINGS, CONTRAINDICATIONS, and PRECAUTIONS sections of the label for Serzone, an antidepressant drug. Rare cases of liver failure leading to transplant and/or death in patients have been reported. A new Patient Package Insert is provided in the product packaging.

Thiazolidinediones [Actos (pioglitazone HCl), Avandia (rosiglitazone maleate)]

Audience: Primary care providers, endocrinologists, cardiologists and other healthcare professionals treating patients with type 2 diabetes mellitus

FDA approved changes to strengthen the labeling for Actos and Avandia. The WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections have been modified to more clearly describe the cardiovascular risks associated with the use of thiazolidinediones as monotherapy and in combination with other antidiabetic agents, particularly insulin.

Zerit (stavudine)

Audience: Healthcare Professionals caring for persons with HIV

FDA and BMS notified healthcare providers caring for persons with HIV of the potential for lactic acidosis as a complication of therapy with Zerit (stavudine), d4T. Reports of occurrences of rapidly ascending neuromuscular weakness, mimicking the clinical presentation of Guillain-Barr syndrome (including respiratory failure), have been reported in HIV-infected patients receiving stavudine in combination with other antiretrovirals. Some cases were fatal. Most of the cases were reported in the setting of lactic acidosis or symptomatic hyperlactatemia.

The early signs and symptoms of clinical events associated with hyperlactatemia should receive careful attention because of the life-threatening potential of the most extreme manifestation, lactic acidosis syndrome (LAS). If motor weakness develops in a patient receiving stavudine, the drug should be discontinued.

Zoloft (sertraline hydrochloride)

Audience: Psychiatrists and other healthcare professionals

At the request of the FDA, Pfizer issued an important drug warning letter announcing that they have added new information to the CONTRAINDICATIONS and PRECAUTIONS sections of the Zoloft labeling, contraindicating the concomitant use of pimozide with sertraline.

Zonegran (zonisamide)

Audience: Neurologists, Pediatricians, and other healthcare professionals

FDA and Elan Pharmaceuticals added a bolded WARNING to inform healthcare professionals that pediatric patients appear to be at an increased risk for zonisamide-associated oligohidrosis and hyperthermia. Patients, especially pediatric patients, treated with Zonegran should be monitored closely for evidence of decreased sweating and increased body temperature, especially in warm or hot weather. The safety and effectiveness of zonisamide in pediatric patients have not been established. Zonisamide is not approved for use in pediatric patients.

Note: **Detailed information on these and other FDA safety alerts is available via the FDA homepage (www.fda.gov).**

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

Sevelamer (Renagel), an oral phosphate binder

- Pegfilgrastim (Neulasta), an injectable colony stimulating factor
- Tacrolimus (Prograf), an injectable immunosuppressive agent (also available in an oral formulation)
- Goserelin depot implant (Zoladex), an injectable synthetic analog of LHRH
- Tamsulosin (Flomax), an oral alpha-$_1$ adrenergic receptor antagonist
- Voriconazole (Vfend), an oral and injectable antifungal agent
- Caspofungin (Cancidas), an injectable echinocandin antifungal
- Itraconazole (Sporanox), an injectable azole antifungal (also available in an oral formulation)

Deletions

- Auranofin 3mg capsules
- Furazolidone oral suspension
- Oxazepam capsules
- Ethinyl estradiol tablets
- Quinidine polygalacturonate tablets
- Procainamide sustained-release tablets

FDA Safety Alerts

- You can access the latest safety information from the Food and Drug Administration website. To access "Dear Health Professional" letters, other safety notifications, and labeling changes related to drug safety, just point your browser to *www.fda.gov* and click on "MedWatch." MedWatch is the FDA's medical products reporting program.
- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov*. In the message body enter: *subscribe medwatch* and your e-mail address.